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TITLE:
Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: a cross-sectional mega-analysis

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ABSTRACT

Background Neuroimaging studies have shown structural alterations in several brain regions in children and adults with attention deficit hyperactivity disorder (ADHD). Through the formation of the international ENIGMA ADHD Working Group, we aimed to address weaknesses of previous imaging studies and meta-analyses, namely inadequate sample size and methodological heterogeneity. We aimed to investigate whether there are structural differences in children and adults with ADHD compared with those without this diagnosis.

Methods In this cross-sectional mega-analysis, we used the data from the international ENIGMA Working Group collaboration, which in the present analysis was frozen at Feb 8, 2015. Individual sites analysed structural T1-weighted MRI brain scans with harmonised protocols of individuals with ADHD compared with those who do not have this diagnosis. Our primary outcome was to assess case-control differences in subcortical structures and intracranial volume through pooling of all individual data from all cohorts in this collaboration. For this analysis, p values were significant at the false discovery rate corrected threshold of p=0·0156.

Findings Our sample comprised 1713 participants with ADHD and 1529 controls from 23 sites with a median age of 14 years (range 4–63 years). The volumes of the accumbens (Cohen's d=–0·15), amygdala (d=–0·19), caudate (d=–0·11), hippocampus (d=–0·11), putamen (d=–0·14), and intracranial volume (d=–0·10) were smaller in individuals with ADHD compared with controls in the mega-analysis. There was no difference in volume size in the pallidum (p=0·95) and thalamus (p=0·39) between people with ADHD and controls. Exploratory lifespan modelling suggested a delay of maturation and a delay of degeneration, as effect sizes were highest in most subgroups of children (<15 years) versus adults (>21 years): in the accumbens (Cohen's d=–0·19 vs –0·10), amygdala (d=–0·18 vs –0·14), caudate (d=–0·13 vs –0·07), hippocampus (d=–0·12 vs –0·06), putamen (d=–0·18 vs –0·08), and intracranial volume (d=–0·14 vs 0·01). There was no difference between children and adults for the pallidum (p=0·79) or thalamus (p=0·89). Case-control differences in adults were non-significant (all p>0·03). Psychostimulant medication use (all p>0·15) or symptom scores (all p>0·02) did not influence results, nor did the presence of comorbid psychiatric disorders (all p>0·5).

Interpretation With the largest dataset to date, we add new knowledge about bilateral amygdala, accumbens, and hippocampus reductions in ADHD. We extend the brain maturation delay theory for ADHD to include subcortical structures and refute medication effects on brain volume suggested by earlier meta-analyses. Lifespan analyses suggest that, in the absence of well powered longitudinal studies, the ENIGMA cross-sectional sample across six decades of ages provides a means to generate hypotheses about lifespan trajectories in brain phenotypes.

Funding National Institutes of Health.

Author's version

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neuropsychiatric disorder with a prevalence of 5·3% in childhood (younger than 18 years old)[1]. Two-thirds of patients with an ADHD diagnosis in childhood continue to have persistent, impairing symptoms in adulthood[2]. ADHD is characterised by age- inappropriate symptoms of inattention or hyperactivity and impulsivity[3]. Many imaging studies, often in small samples, have reported brain structural and functional differences between individuals with ADHD and controls, both in childhood and adulthood. Five meta- analyses of structural neuroimaging studies in patients with ADHD have been published (appendix). One meta-analysis pooled region-of-interest brain volume studies[4], whereas the others pooled voxel-based morphometry studies[5–8]. The most consistent results across studies were for reduced volumes of (parts of) the basal ganglia for patients compared with healthy controls. Two meta- analyses showed that, with increasing age, basal ganglia structural differences between individuals with ADHD and controls tended to decrease, and that stimulant treatment was associated with healthy volumes of these brain structures[5,6].

Altered brain volumes have also been associated with clinical features of ADHD; smaller volumes of caudate, cerebellum, and frontal and temporal gray matter have been associated with greater symptom severity[9]. Also in the general population, ADHD symptoms correlated with volumetric brain measures[10,11].

Identification of structural brain differences in people with ADHD is important to further insights into the neural substrates of ADHD. So far, analyses of brain structures in ADHD have been small in size and statistical power (appendix); the sample size of the largest published meta-analysis of brain volume (565 cases and 583 controls) allowed for the identification of differences in brain volume with Cohen's d effect sizes of 0·15 or higher with 80% power (G*Power, version 3.1). Analyses of other psychiatric disorders show that smaller effects are likely[12]. Existing meta-analyses for ADHD only used published data as source material, which limited their ability to address covariates that might vary among studies, such as age and medication[5,6]. Additionally, the existing meta-analyses included studies with variable methods and protocols such as the segmentation software and quality control.

To overcome such limitations and to do collaborative studies of maximal power, we founded the ENIGMA ADHD Working Group in 2013 to aggregate structural MRI data from participants with ADHD and healthy controls across the lifespan. This worldwide collaboration enabled analyses of existing individual data, improving on earlier meta-analyses by basing analyses on the use of harmonised segmentation and quality control protocols. Our increased sample size compared with all earlier studies supported both mega-analysis and meta-analysis (appendix) designs across 60 years of the lifespan. We selected subcortical brain volumes as our target, because of neurodevelopmental theories hypothesising that ADHD is linked to early-emerging, persistent subcortical abnormalities[13], and building on the results of earlier meta-analyses[4–8], which showed that deviations in these subcortical volumes were most consistently observed. Additionally, we investigated intracranial volume as a measure of total brain volume. The mega-analysis design allowed investigation of associations with symptom scores, age, psychostimulant medication use, and comorbidity with other psychiatric disorders.

Methods

Study design

This cross-sectional mega-analysis was done with the ENIGMA ADHD Working Group; details about the diagnostic procedures for each site are listed in the appendix. The group adopted a rolling inclusion design, in which new groups can join at any time, but data freezes allowed for analysis at fixed timepoints. The data freeze for the present subcortical analysis was set at Feb 8, 2015. Each participating site had approval from its local ethics committee to do the study and to share de-identification anonymised individual data. Part of the protocol is published online.

Neuroimaging

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Structural T1-weighted brain MRI data were acquired and processed at the individual sites. The images were analysed with standardised protocols to harmonise analysis and quality control processes (appendix)[14]. We used fully- automated and validated neuroimaging segmentation algorithms based on FreeSurfer versions 5.1 or 5.3 (appendix). To make sure FreeSurfer version did not affect the results[12], we did an additional analysis, adding version number as a covariate to our main model. For each participant, we computed intracranial volume and left and right volumes of the accumbens, putamen, pallidum, caudate, thalamus, amygdala, and hippocampus. For further analysis, we used the mean of the left and right volume. For an overview of single site subcortical structures, see appendix. Outliers were identification at above and below one and a half times the interquartile range per cohort and group (case and control) and were excluded (appendix)[15].

Differences in subcortical brain volumes and intracranial volume

By pooling available individual data from all cohorts in a mega-analysis, we were able to investigate as our primary outcome differences between cases and controls of subcortical volumes and intracranial volume. After excluding collinearity of age, sex, and intracranial volume (variance inflation factor <1·2) and normality testing, the mega-analysis of each subcortical volume was done with a linear mixed model with the package nlme in R (version 3.1-117). The model included diagnosis (case=1 and control=0) as a factor of interest, age, sex, and intracranial volume as fixed factors, and site as a random factor. In the analysis of intracranial volume, this variable was omitted as a covariate from the model. Handedness was added to the model to correct for possible effects of lateralisation, but was excluded from the model when there was no significant contribution of this factor. To calculate Cohen's d effect size estimates, adjusted for age, sex, site, and intracranial volume, we used the t statistic from the factor diagnosis in the model. In a post-hoc analysis, left and right volumes were studied separately.

To make sure that no unobserved factor biased our analysis of case-control diff a meta-analysis was also done by linear regression analysis for each volume and for each sample separately, taking age, sex, and intracranial volume into account. We characterised heterogeneity with the I^2 statistic. The R package metaphor (version 1.9-1) was used to do an inverse variance-weighted, random-eff meta-analysis, in accordance with other ENIGMA Working Groups (appendix)[12,15].

Effects of age

The prespecified secondary outcome of the effects of age on subcortical volume and intracranial volume was studied by running the above described model for groups stratification by age: in children aged 14 years or younger, adolescents aged 15–21 years, and adults aged 22 years and older. We removed samples that were left with ten patients or fewer because of the stratification. Because the effect of age probably do not strictly follow a linear model, we report linear effect of age and the effect of age by diagnosis. More explorative modelling was done to better understand the effects of age, by plotting of moving averages and use of fractional polynomials to fi non-linear models to the data (appendix).

Corrections for multiple comparisons for 32 tests (eight volumes and four groups: all, children, adolescents, and adults) were applied by use of a false discovery rate with q=0·05, resulting in a p-value significance threshold of p=0·0156.

Effects of sex, psychostimulant medication, and clinical measures

In an exploratory analysis, we investigated the effects of sex on brain volume from the main model. To examine associations between previous psychostimulant treatment and regional brain volume, the mega-analysis model was run again, including only patients with medication information available (appendix). To test whether acute effects of psychostimulant medication confounded possible brain-volume differences between participants with ADHD and healthy controls, we excluded patients treated with stimulants at the time of their participation in the study (participants receiving other types of treatment were retained). Additionally, as previous meta-analyses had shown an association between stimulants and brain volumes[5,6], we compared patients who had ever

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used stimulant medication to patients who had never used stimulant medication. We explored the effects of ADHD symptom scores and the presence or absence of comorbid disorders on those brain volumes that differed significantly between participants with ADHD and healthy controls (appendix).

Role of funding sources

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data and the fi responsibility to submit for publication.

Results

We included data from 23 cohorts with a sample size of 3242 (1713 participants with ADHD and 1529 healthy controls; table 1) and a median age of 14·0 (range 4–63) years. As shown in table 2, the mega-analysis indicated that participants with ADHD had significantly smaller volumes for the accumbens, amygdala, caudate, hippocampus, putamen, and intracranial volume. Post-hoc analyses for the subcortical regions showed these eff to be bilateral (appendix). No effects of FreeSurfer version or handedness was recorded (appendix).

Results of the case-control meta-analysis were largely similar to those of the mega-analysis, but volume differences for accumbens and hippocampus were not significant (appendix). Heterogeneity (I^2) across samples was low to moderate; heterogeneity was highest for the hippocampus (appendix) and might be indicative of non-linear effects of study site for this structure.

Age-stratified analyses showed significant case-control differences in children for the accumbens, amygdala, caudate, hippocampus, putamen, and intracranial volume (table 3, figure 1). Effect sizes were higher in children than those for the entire sample. In the adolescent group, there was a significant case-control difference in the hippocampus (table 3). In adults, none of the case-control comparisons were significant. Figure 1 suggested an interaction effect for age-group and diagnosis on hippocampus volume; this was not statistically supported by linear interaction statistics (p=0·03; appendix). Exploratory modelling with moving averages also showed that the age effects cluster early in life, with older age participants attaining peak volumes in the ADHD group (figure 2). The moving averages also suggested a potential later onset of volume decrease in the ADHD group, most clearly seen in accumbens and putamen (figure 2). Sample sizes after age 50 years were small (appendix), and resulted in wider confidence intervals in the moving average analyses. The fractional polynomial analyses also supported different develop- mental models for patients with ADHD and controls for amygdala, hippocampus, putamen, thalamus, and intracranial volume (appendix).

All but two subcortical structures, accumbens and caudate, showed effects of sex in the mega-analysis (table 2). None of the volumes showed differential sex effects for participants with ADHD and controls (table 2). Information about medication use was available for 1254 (73%) of 1713 participants with ADHD; 455 (27%) of 1713 participants with ADHD were on psychostimulant medication (methylphenidate or amphetamine) at the time of scanning, with more than half (19 [83%] of 23) of the studies with a washout period of 24 h or 48 h (appendix); 799 (47%) of 1713 participants with ADHD were not taking stimulant medication at scan time. Case- control differences in brain volumes after excluding participants on stimulant medication were similar in effect sizes to those observed in the main analysis (table 4).

For 719 (42%) of 1713 participants with ADHD, information was available on lifetime usage of stimulant medication. Of these, 82 (11%) participants had never taken stimulant medication, compared with 637 (89%) patients, who used stimulant medication somewhere in their lifetime for a period of more than 4 weeks. No differences in any of the volumes were recorded by directly comparing these two groups.

Meta-analysis of the correlation between ADHD symptom scores in cases and brain volumes showed no significant effects (p>0·02; appendix). Nor were there any significant correlations when only the childhood samples were used in the meta-analysis. Also, the observed case- control brain volume differences were not explained by the presence of another comorbid psychiatric disorder (p>0·5; appendix).

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Discussion

We report the largest study to date of brain volume differences between participants with ADHD and healthy individuals. Compared with previous meta-analyses, our study newly identified amygdala, accumbens, and hippocampus volumes to be smaller in participants with ADHD than in healthy controls, and extended earlier findings for reduced caudate and putamen volumes by showing those effects to be bilateral rather than unilateral[5,7]. Significant volume differences had small effect sizes (ranging from d=–0·10 to d=–0·19) and the meta-analysis confirmed these results. Age stratification showed that volume differences clustered in children and no differences were reported in adults. The volume differences were equally apparent in those treated with psychostimulant medication and in those naive to psychostimulants. Additionally, no correlations with quantitative scores of ADHD symptoms were reported in cases, nor did comorbidity with other psychiatric disorders explain the findings. All but two subcortical brain volumes were smaller in women; this is consistent with published literature[16].

Our findings contain several important messages for clinicians. First, the data from our highly powered analysis confirm that patients with ADHD do have altered brains and therefore that ADHD is a disorder of the brain. This message is clear for clinicians to convey to parents and patients, which can help to reduce the stigma that ADHD is just a label for difficult children and caused by incompetent parenting. We hope this work will contribute to a better understanding of ADHD in the general public, and that it becomes as apparent as major depressive disorder, for example, that we label ADHD as a brain disorder. Second, finding the most pronounced effects in childhood and showing delayed peaks of subcortical volume maturation provides a relevant model of ADHD as a disorder of brain maturation delay. Third, the brain differences we have reported are not caused by any comorbid disorders, medication effects, or ADHD symptom severity, but are exclusively related to the ADHD diagnosis. Fourth, finding the largest effect in the has been associated with amygdala is important because this region links ADHD to emotional regulation problems. Those symptoms are often present in patients with ADHD, but these disease characteristics have not (yet) been included into the official DSM criteria. Our work provides neurobiological support for the inclusion of this domain in the core ADHD phenotype, asking for more acknowledgement of the importance of emotional regulation problems in patients with ADHD.

Our findings for striatum volume reduction are consistent with present models of ADHD[17]. Differences in caudate volume are the most consistent finding[4-6] and smaller putamen volumes have been frequently reported[5,7].

Our study provides robust effect size estimates for those structural differences and shows that effects are bilateral. Although identified before in one study[18], our findings extend the meta-analytics literature to the third striatal volume, the nucleus accumbens. We identified novel meta-analytical findings for the amygdala and hippocampus. Previous work in single studies had found effects in these structures[19–21], but did not replicate in others[22,23]. For amygdala volume, which showed the largest effect size in our study (d=–0·19 in the whole cohort; d=–0·18 in children), and for accumbens, the scarcity of earlier meta-analytical evidence for its role in ADHD might be due to the fact that these are small structures, for which automatic segmentation does less well[24]. A more highly powered analysis might therefore have been necessary to overcome the experimental inaccuracy of these measures. Previous work provides functional evidence for a role of amygdala, accumbens, and hippocampus in patients with ADHD. Dysfunction of the amygdala is associated with difficulties in recognition of emotional stimuli, in callous unemotional traits, and with emotional regulation in general[25,26]. Difficulties in recognition of emotional stimuli, diminished emotional reactions to pleasant stimuli, and high levels of callous, unemotional traits have all been linked to ADHD[27–30], and amygdala volume has been associated with hyperactivity[29]. The accumbens, with its prominent role in reward processing, is central to motivational and emotional dysfunction in patients with ADHD[17]. The results of the hippocampus are less straight-forward, because there is not so much evidence for a deficit in long-term memory, the main function of the hippocampus, in patients with ADHD[31]. However, there are also reports on the hippocampus having a role in the regulation of motivation and emotion, which is impaired in patients with ADHD[32].

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Importantly, effect sizes observed in our study were similar to those reported for other psychiatric disorders analysed with the ENIGMA procedures, in particular major depression and bipolar disorder[12,33]. The scale of the effects is consistent with expectations for a heterogeneous disorder such as ADHD. The specific pattern of findings might partially differentiate ADHD from the other psychiatric disorders analysed with similar procedures, ie, schizophrenia, bipolar disorder, and major depressive disorder[12,14,33]. In particular, effects on caudate and putamen seem to be ADHD specific among the four disorders. However, as mostly adults were assessed for the other three disorders, formal analyses taking age into account will need to be done to make valid statements.

The results of the age-stratified analysis indicate that subcortical volume differences in ADHD are most prominent in children, and non-existent in adults. Our additional exploratory models suggest that this finding is not the entire story on age effects, although care in interpretation of this result is needed because of the cross-sectional design of this study. On the basis of our findings across different approaches, we propose a model of altered trajectories of subcortical volume in patients with ADHD. Our data suggest a delayed peak volume in participants with ADHD, which is reminiscent of earlier reports that showed altered velocity of cortical development in a longitudinal sample[34]. This model should be confirmed by longitudinal analyses, especially because the childhood and adult ADHD samples included in this study represent different subgroups of the population: childhood ADHD samples include those who will later remit and those who will persist having ADHD in adulthood; the adult ADHD samples include only the latter. In addition to the delays in subcortical brain maturation at early age, our exploratory work tentatively suggests later onset of decreases in subcortical volumes beyond the fourth decade of life in ADHD. However, because sample sizes in our analysis dropped dramatically above age 25 years, and we had insufficient data to study age effects after 60 years, this work is hampered by not having sufficient patients per site to rule out site-biases in those age ranges. As long as ADHD in old age is still a blind spot in ADHD research, it will be difficult to test the validity of such findings.

Previous meta-analyses showed associations between the proportion of treated patients and right caudate and amygdala and uncus (an anterior extremity of the parahippocampal gyrus) volumes[5,6]. In our analysis, in which we were able to compare treated to non-treated participants with ADHD directly in a sample more than four times larger than that of the samples in two previous meta-analyses[5,6], we did not confirm such associations with brain volume. Our findings support those of the most recent meta-analysis[6]. However, because our study had a non-randomised, cross-sectional design, some caution in the interpretation of these results is warranted because the design of this study was not optimal to test for medication effects. Also, because both previous meta-analyses used voxel-wise maps, there is a possibility that the observed normalising effects of medication were too local to be picked up by volumetry.

We did not note associations between brain volumes and clinical measures, ie, comorbidity or ADHD symptom scores. The absence of an association with comorbidity suggests that the brain volume reductions are robustly linked to ADHD itself, rather than being a secondary phenomenon caused by comorbidity. The absence of significant associations between brain volumes and symptom ratings is not surprising, given that brain function is based on distributed networks of brain regions rather than individual brain regions[35]. Still, previous studies did find single volume–function associations[9,36], which we do not replicate here. We also could not replicate an earlier reported (modest) correlation of a total brain volume measure highly related to intracranial volume with ADHD symptom severity in a similarly sized population sample[10]. Not finding effects of symptom scores might also be due to the heterogeneity of the instruments used for different cohorts in our study or differences in raters (ie, clinicians, teachers, and parents). Additionally, the sample size was halved in this case-only analysis, and the distribution of scores was skewed to the clinical range. In agreement with models of frontostriatal dysfunction in patients with ADHD, one hypothesis could be that cortical structures have a more important role in the severity of symptoms in these patients than the subcortical structures[13].

A clear strength of this study is the sample size, being the largest mega-analysis and meta-analysis to date, with enough power to detect effects as small as d=0·08. Another strength is the harmonisation

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of segmentation protocols across all contribution sites, reducing imprecision caused by differences in methods. Nonetheless, diagnostic routines and acquisition of imaging data still differ between sites, a limitation contributing to heterogeneity across samples. A strength was also the opportunity for mega-analysis. Although effect sizes were similar to the meta-analysis, the mega-analysis allowed a more powerful detection of case-control volume differences. The mega- analysis also enabled effects of age, sex, comorbidity, and medication to be studied, although accounting for site in these analyses might have somewhat masked age effects (as many studies had a restricted age range). Modelling age in a cross-sectional study is challenging but we have used several approaches to understand the effect of age. However, we should be cautious and interpret our findings as hypothesis-generating for future studies.

To conclude, these data are the first results of our worldwide collaboration and confirm and extend previous findings of reduced striatal volume in patients with ADHD. Optimisation of sample size and harmonisation of methods across studies allowed us to identify additional differences in amygdala and hippocampal volumes between cases and controls, potentially contributing to problems in emotional regulation, motivation, and memory in patients with ADHD. Brain volume differences were most prominent in children. We invite interested researchers to join the next studies of the ENIGMA ADHD Working Group. In this way, we might optimally benefit from efforts already invested in individual studies to better understand this common yet still vexing disorder.

Contributors

MH, JB, DPH, MM, MPZ, LSJS, KJEvH, SEM, ES, NJ, SVF, PMT, and BF designed the protocol, and did the quality testing and analysis. All authors took part in the data collection, processing, analysis, or funding. MH, JB, MM, MPZ, ES, PS, PMT, SVF, and BF prepared the manuscript. All authors contributed edits and approved the content of the manuscript.

Declaration of interests

TGMvE consulted for Roche Pharmaceuticals and has a contract with Otsuka Pharmaceutical, Ltd. AD is a founder of CorTechs Labs, Inc and is on the Scientific Advisory Boards of CorTechs Labs and Human Longevity, Inc., and receives research funding through a Research Agreement with General Electric Healthcare. PM was on the speakers' bureau or acted as consultant for Janssen-Cilag, Novartis, and Shire in the previous 5 years; he also received travel awards to participate in scientific meetings from those companies. The ADHD outpatient programme (Grupo de Estudos do Déficit de Atenção/Institute of Psychiatry) chaired by PM has also received research support from Novartis and Shire. TB served in an advisory or consultancy role for Hexal Pharma, Lilly, Medice, Novartis, Oxford outcomes, PCM scientific, Shire, and Viforpharma. He received conference support or speaker's fee by Janssen McNeil, Lilly, Medice, Novartis, and Shire. He is or has been involved in clinical trials done by Shire and Viforpharma, outside of this paper. KR received speaker's fees form Shire and Medice, and a grant from Lilly for another project. JH has received speaker fees from Lilly, Novartis, and Janssen Cilag. SVF has received income, travel expenses or research support from, has been on an advisory board for, or participated in continuing medical education programmes sponsored by: Pfizer, Ironshore, Shire, Akili Interactive Labs, CogCubed, Alcobra, VAYA Pharma, Neurovance, Impax, NeuroLifeSciences, Otsuka, McNeil, Janssen, Novartis, Eli Lilly, and the National Institutes of Health (NIH). With his institution, SVF has a US patent (US20130217707 A1) for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. SVF also receives royalties from books published by Guilford Press, Oxford University Press, and Elsevier. JB receives research support from the following sources: The Department of Defense, US Food and Drug Administration, Ironshore, Lundbeck, Magceutics Inc., Merck, PamLab, Pfizer, Shire Pharmaceuticals Inc., SPRITES, Sunovion, Vaya Pharma/Enzymotec, and NIH. JB received honoraria from the MGH Psychiatry Academy for tuition-funded continuing medical education courses. He has a US patent application pending (provisional number #61/233,686) through Massachusetts General Hospital corporate licensing, on a method to prevent stimulant abuse. JB received honoraria from the MGH Psychiatry Academy for tuition-funded continuing medical education courses. He received research support from AACAP,

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Tables

Table 1. Overview of cohort characteristics by sample

Site	Country of origin	Total (n=3242)	Cases (n=1713)		Controls (n=1529)		Age	Age SD
			Men	Women	Men	Women		
ADHD-WUE	Würzburg, Germany	118	32	30	26	30	39·7	(11·4)
ADHD-DUB1	Dublin, Ireland	75	27	9	31	8	22·3	(5·2)
ADHD-DUB2	Dublin, Ireland	20	16	4	..	..	33·7	(10·2)
ADHD-Mattos	Rio de Janeiro, Brazil	17	10	7	..	..	22·9	(1·4)
ADHD200-KKI	Baltimore, USA	94	15	10	41	28	10·2	(1·3)
ADHD200-NYU*	New York, USA	260	115	36	54	55	11·5	(2·9)
ADHD200-Peking	Peking, China	245	90	12	84	59	11·7	(2·0)
ADHD200-OHSU	Oregon, USA	109	29	13	30	37	9·1	(1·3)
ADHD-UKA	Aachen, Germany	181	95	7	53	26	11·2	(2·7)
Bergen-adultADHD	Bergen, Norway	81	21	17	16	27	31·2	(6·7)
Bergen-SVG	Bergen, Norway	54	20	5	20	9	10·1	(1·2)
DAT-London London	London, UK	56	27	0	29	0	15·8	(2·1)
IMpACT-NL	Nijmegen, Netherlands	245	49	76	49	71	35·5	(11·4)
MGH-ADHD	New York, USA	148	42	37	29	40	35·8	(12·0)
NICHE	Utrecht, Netherlands	158	68	10	67	13	10·4	(2·00)
NYU ADHD	New York, USA	80	22	18	22	18	31·6	(9·4)
UAB-ADHD	Barcelona, Spain	198	82	21	64	31	25·8	(13·0)
ZI-CAPS	Mannheim, Germany	35	17	5	7	6	12·7	(1·2)
ADHD-Rubia	London, UK	77	44	0	33	0	14·0	(2·2)
NeuroImage-ADAM Amsterdam	Amsterdam, Netherlands	182	73	24	57	28	17·2	(3·2)
NeuroImage-NIJM	Nijmegen, Netherlands	178	89	50	23	16	16·9	(3·4)
NIH	Bethesda, USA	502	168	83	168	83	10·0	(3·1)
MTA	Irvine, USA	129	73	15	31	10	25·6	(1·4)

Data are n or mean (SD). For a more detailed description and references for the assessments and neuroimaging procedures, see appendix. *One patient was excluded because of a missing sex status.

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Table 2. Results of the mega-analysis of subcortical brain volumes in the total sample

	Cases (n=1713)	Controls (n=1529)	p value for diagnosis	Cohen's *d**	(95%CI)	Other significant factors in the model
Accumbens	1652	1471	<0·0001†	–0·15	(–0·22 to –0·08)	Intracranial volume, site, age
Amygdala	1598	1463	<0·0001†	–0·19	(–0·26 to –0·11)	Sex, intracranial volume, site
Caudate	1659	1489	0·0014†	–0·11	(–0·18 to –0·05)	Intracranial volume, site, age
Hippocampus	1599	1436	0·0041†	–0·11	(–0·18 to –0·03)	Sex, intracranial volume, site
Pallidum	1651	1471	0·95	–0·00	(–0·07 to 0·07)	Sex, intracranial volume, site, age
Putamen	1660	1497	<0·0001†	–0·14	(–0·21 to –0·07)	Sex, intracranial volume, site, age
Thalamus‡	1405	1242	0·39	–0·03	(–0·04 to 0·11)	Sex, intracranial volume, site, age
Intracranial volume	1693	1513	0·0065†	–0·10	(–0·17 to -0·03)	Sex, site, age

*Adjusted mean volumes of subcortical brain volumes by site are described in the appendix. †p values are significant at the false discovery rate corrected threshold of p=0·0156. ‡Thalamus volume was not available from the National Institutes of Health sample.

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Table 3. Results of the mega-analysis of subcortical brain volumes in the stratified age groups

	Children (<15)			Adolescents (15-21)			Adults (21>)		
	N Cases/ Controls	**p-value for *Diagnosis***	**Cohen's *d* *(95%CI)***	**N Cases/ Controls†**	**p-value for *Diagnosis***	**Cohen's *d* *(95%CI)***	**N Cases/ Controls**	**p-value for *Diagnosis***	**Cohen's *d* *(95%CI)***
Accumbens	810/827	**0·0001**	-0·19 (-0·29 to -0·10)	323/224	0·61	-0·04 (-0·22 to 0·12)	510/415	0·12	-0·10 (-0·23 to -0·03)
Amygdala	767/820	**0·0003**	-0·18 (-0·28 to -0·08)	321/226	0·12	-0·14 (-0·31 to 0·03)	500/412	*0·03*	-0·14 (-0·27 to -0·01)
Caudate	825/840	**0·006**	-0·13 (-0·23 to -0·04)	324/224	0·28	-0·10 (-0·27 to 0·07)	502/420	0·30	-0·07 (-0·20 to 0·05)
Hippocampus	764/802	**0·012**	-0·12 (-0·22 to -0·03)	320/225	**0·006**	-0·24 (-0·42 to -0·08)	506/404	0·38	0·06 (-0·07 to 0·19)
Pallidum	816/831	0·79	-0·01 (-0·11 to 0·08)	321/223	0·78	0·02 (-0·15 to 0·20)	506/412	0·51	0·04 (-0·08 to 0·17)
Putamen	836/854	**0·0002**	-0·18 (-0·28 to -0·09)	329/228	0·83	-0·02 (-0·19 to 0·15)	499/416	0·23	-0·08 (-0·21 to 0·05)
Thalamus[#]	604/616	0·89	0·01 (-0·10 to 0·06)	288/202	0·74	0·03 (-0·15 to 0·21)	503/416	0·28	-0·07 (-0·20 to -0·06)
ICV	837/854	**0·003**	-0·14 (-0·24 to -0·04)	330/229	0·13	-0·13 (-0·30 to 0·04)	515/422	0·91	0·01 (0·06 to -0·12)

Bold p-values are significant at the FDR-corrected threshold of p=0·0156, [#]thalamus volume was not available from the NIH sample. † Due to a sample size lower than 10, the data for the following cohorts in analysis of the adolescent group were omitted: ADHD-Mattos (n=2), ADHD-WUE (n=2), BergenAdultADHD (n=4), MTA (n=2), Niche (n=7), ZI-CAPS (n=2).

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Table 4. Results of the exploration of the effect of medication on case-control differences

	Patients currently not taking stimulants versus controls*			**Stimulant use in patients: positive versus negative lifetime history**	
	n Cases/ Controls	**Cohen's *d (95%CI)***	**p-value for *Diagnosis***	**n Never / ever stimulant use in patients only**	**p-value for positive versus negative for lifetime stimulant use**
Accumbens	776/1484	-0·12 (-0·21 -0·03)	0·007	79/625	0.32
Amygdala	753/1474	-0·18 (-0·27 to -0·10)	$4{\cdot}90x10^{-9}$	80/590	0.41
Caudate	777/1502	-0·10 (-0·19 to -0·01)	0·02	80/627	0.15
Hippocampus	757/1446	-0·08 (-0·17 to 0·003)	0·06	80/593	0.69
Pallidum	776/1484	0·01 (-0·07 to 0·10)	0·74	79/621	0.26
Putamen	784/1508	-0·13 (-0·22 to -0·04)	0·004	81/627	0.29
Thalamus	692/1253	-0·03 (0·04 to -0·12)	0·53	80/458	0.29
ICV	793/1512	-0·06 (0·04 to -0·16)	0·15	81/632	0.92

*Within this group, 152 subjects were lifetime positive for the use of stimulant medication, 82 were lifetime negative; for 565 no lifetime information was available.

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Figure legends

Figure 1: Cohen's *d* effect sizes of differences between patients with ADHD and healthy controls for subcortical volumes and intracranial volume, for all patients, children only (<15 years), adolescents only (15–21 years), and adults only (>21 years)
Error bars denote standard error. ICV=intracranial volume.

Figure 2: The moving averages, corrected for age, sex, intracranial volume, and site for the subcortical volumes. Error bars denote standard error.

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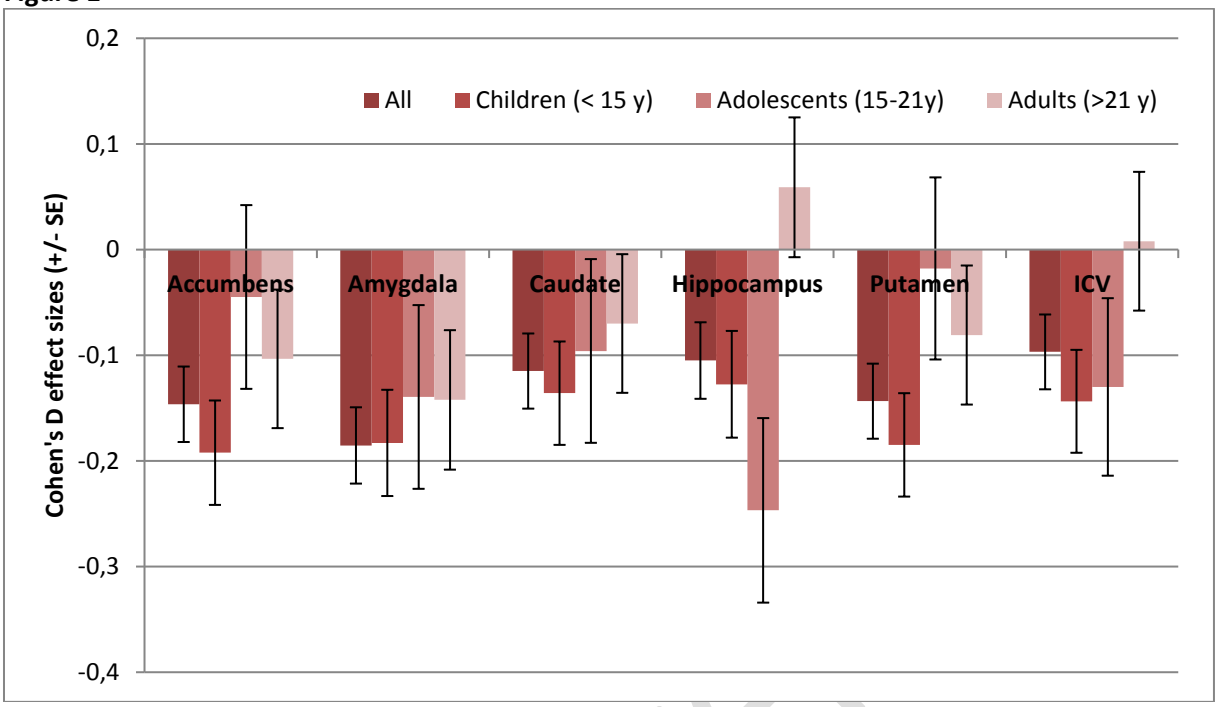
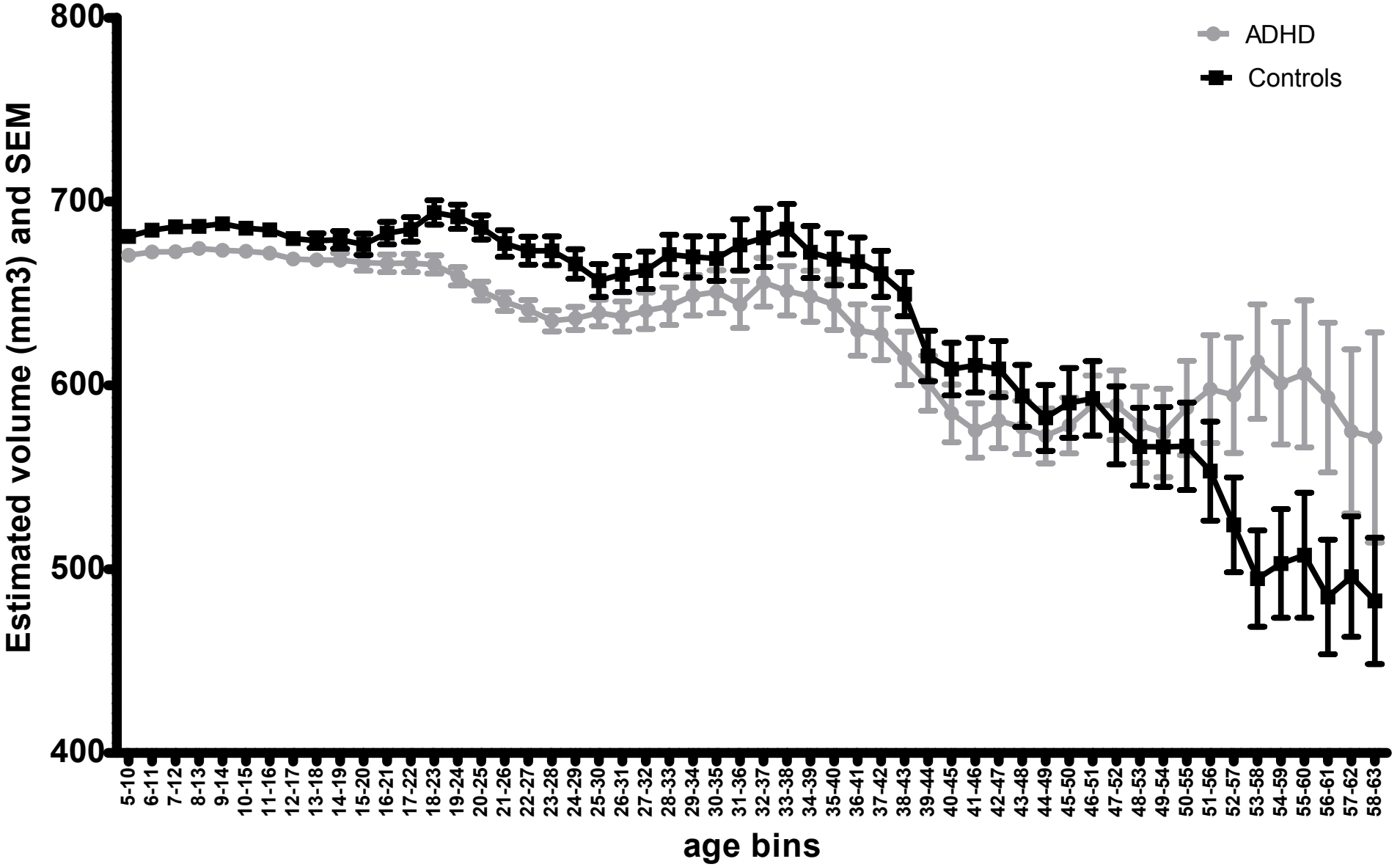
Figures

Figure 1



Authors ver

Accumbens


ADHD
Controls
Estimated volume (mm3) and SEM
800
700
600
500
400
5-10
6-11
7-12
8-13
9-14
10-15
11-16
12-17
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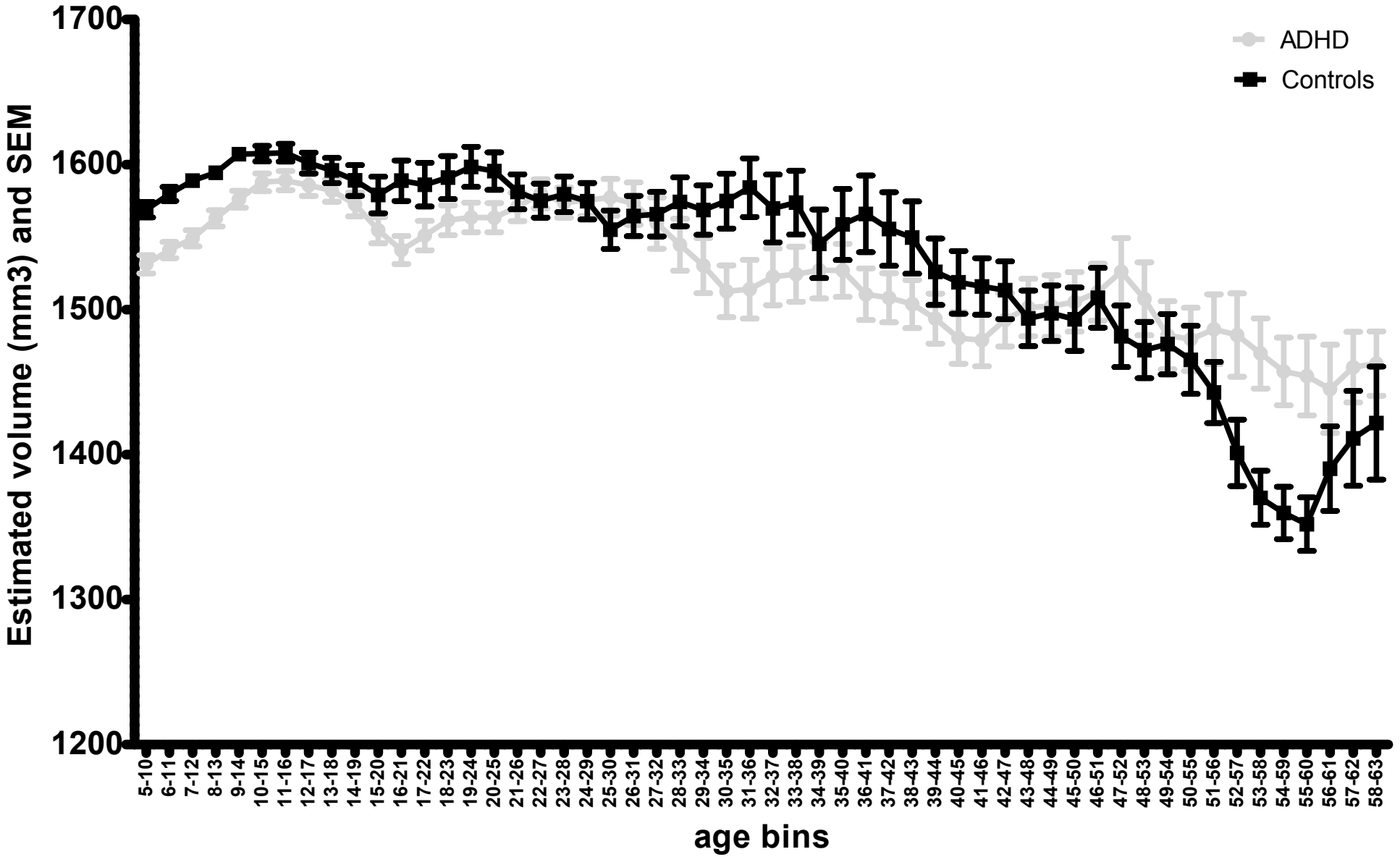
56-61
57-62
58-63
age bins

Amygdala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Controls
Estimated volume (mm3) and SEM
1700
1600
1500
1400
1300
1200
5-10
6-11
7-12
8-13
9-14
10-15
11-16
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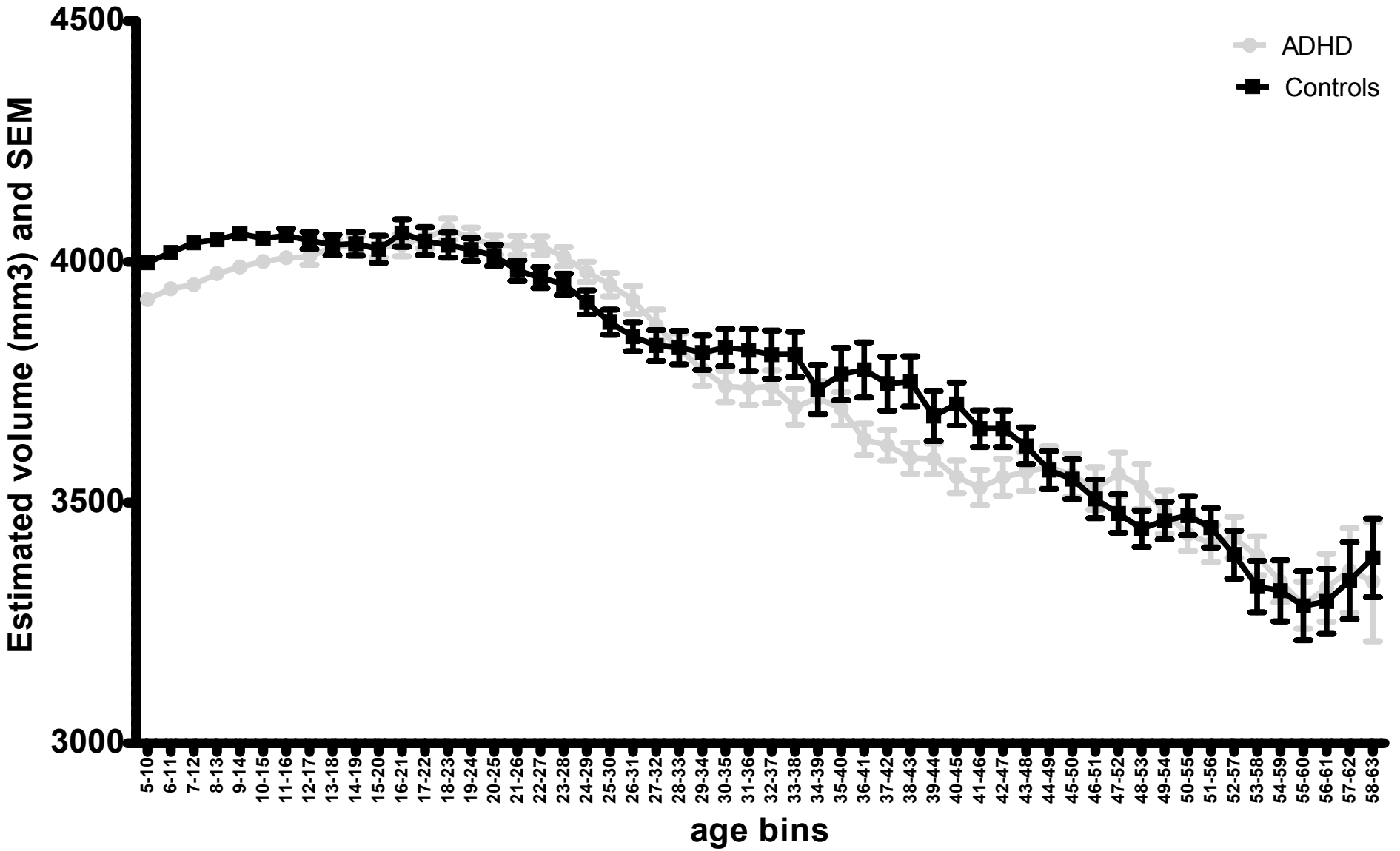
56-61
57-62
58-63
age bins

Caudate


ADHD
Controls
Estimated volume (mm3) and SEM
4500
4000
3500
3000
5-10
6-11
7-12
8-13
9-14
10-15
11-16
12-17
13-18
14-19
15-20
16-21
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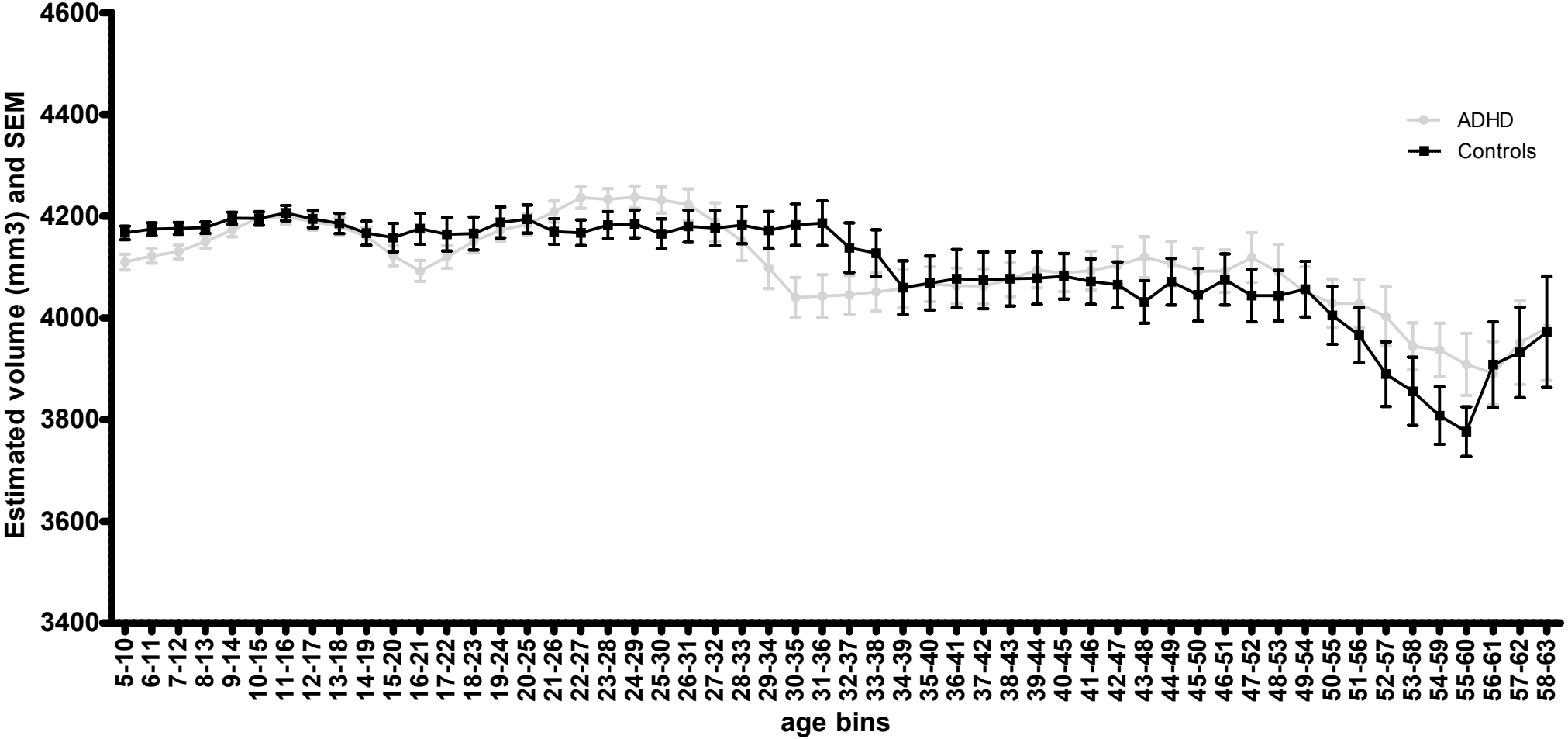
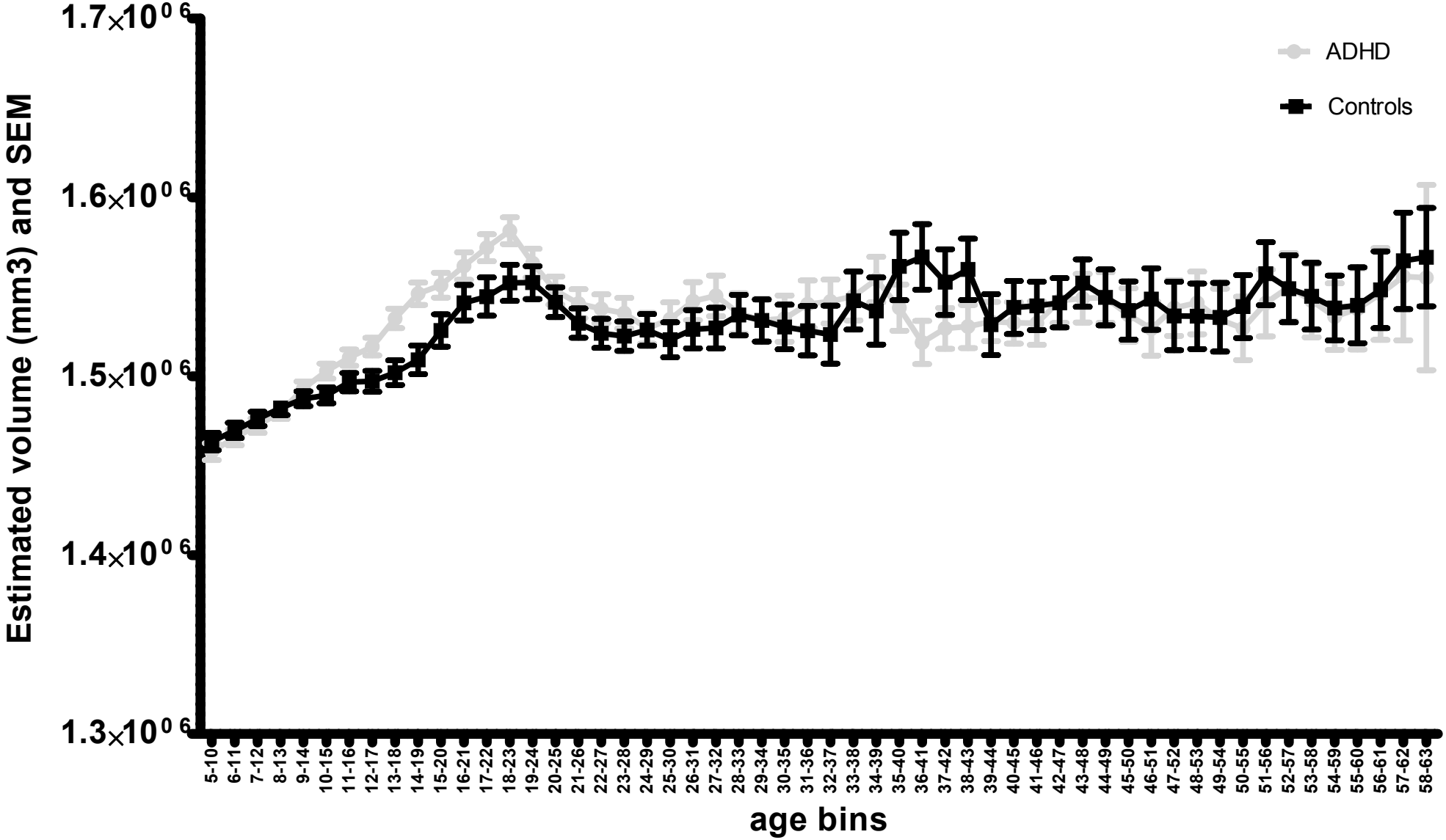
57-62
58-63
age bins

Hippocampus



ICV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Controls
Estimated volume (mm3) and SEM
1.7×10^0 6
1.6×10^0 6
1.5×10^0 6
1.4×10^0 6
1.3×10^0 6
5-10
6-11
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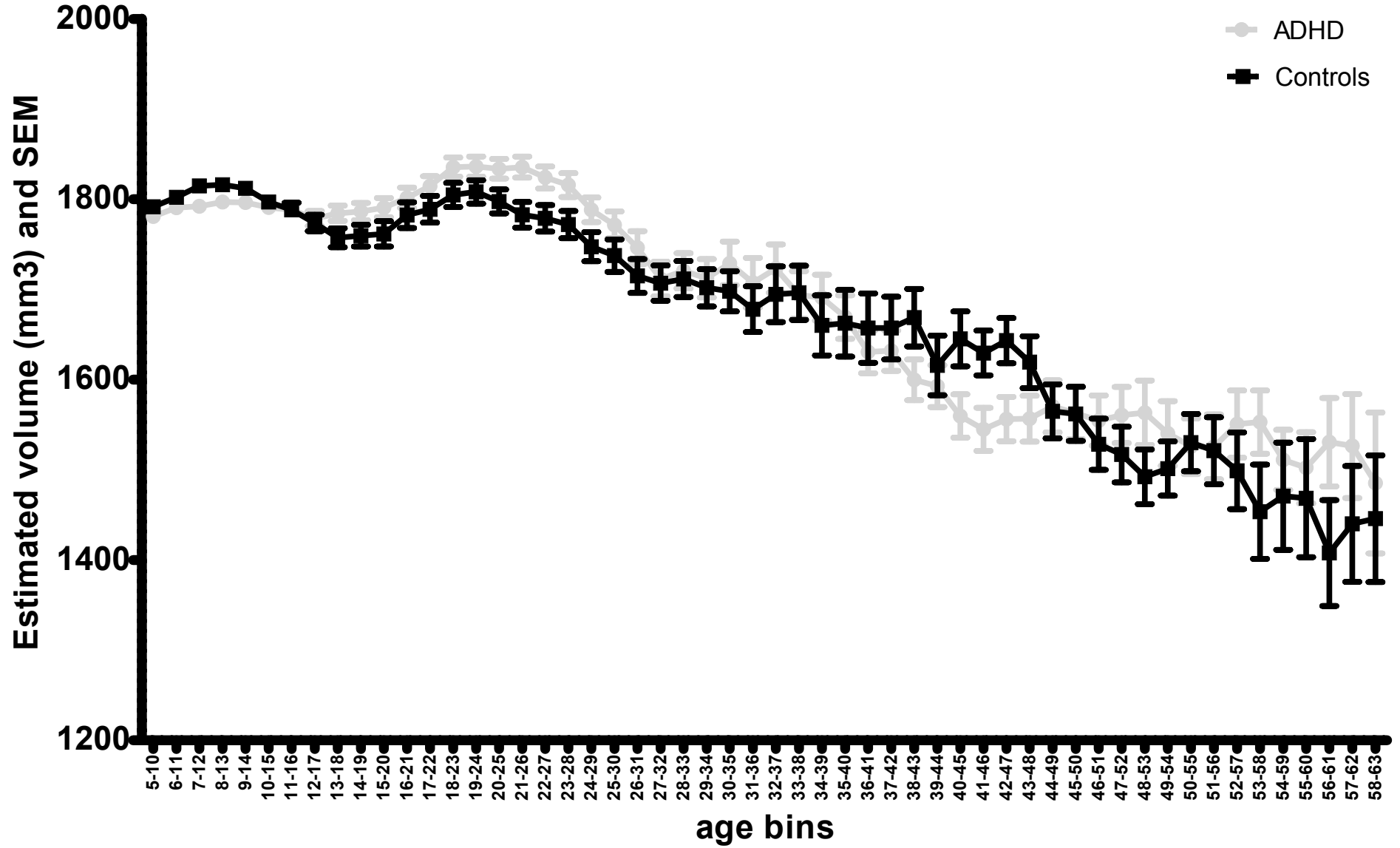
age bins

Pallidum


ADHD
Controls
Estimated volume (mm3) and SEM
2000
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1600
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1200
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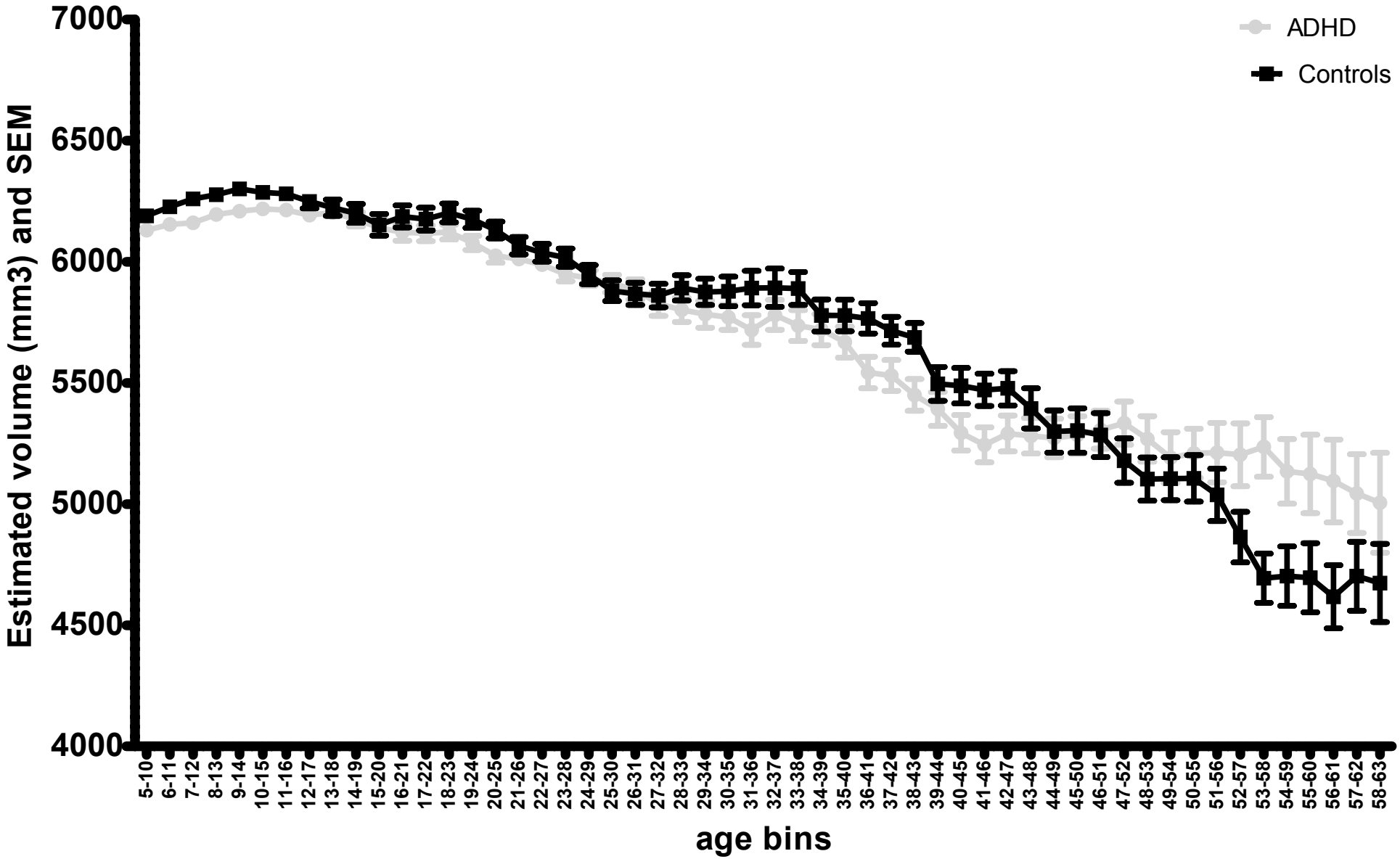
age bins

Putamen


ADHD
Controls
Estimated volume (mm3) and SEM
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6500
6000
5500
5000
4500
4000
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6-11
7-12
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9-14
10-15
11-16
12-17
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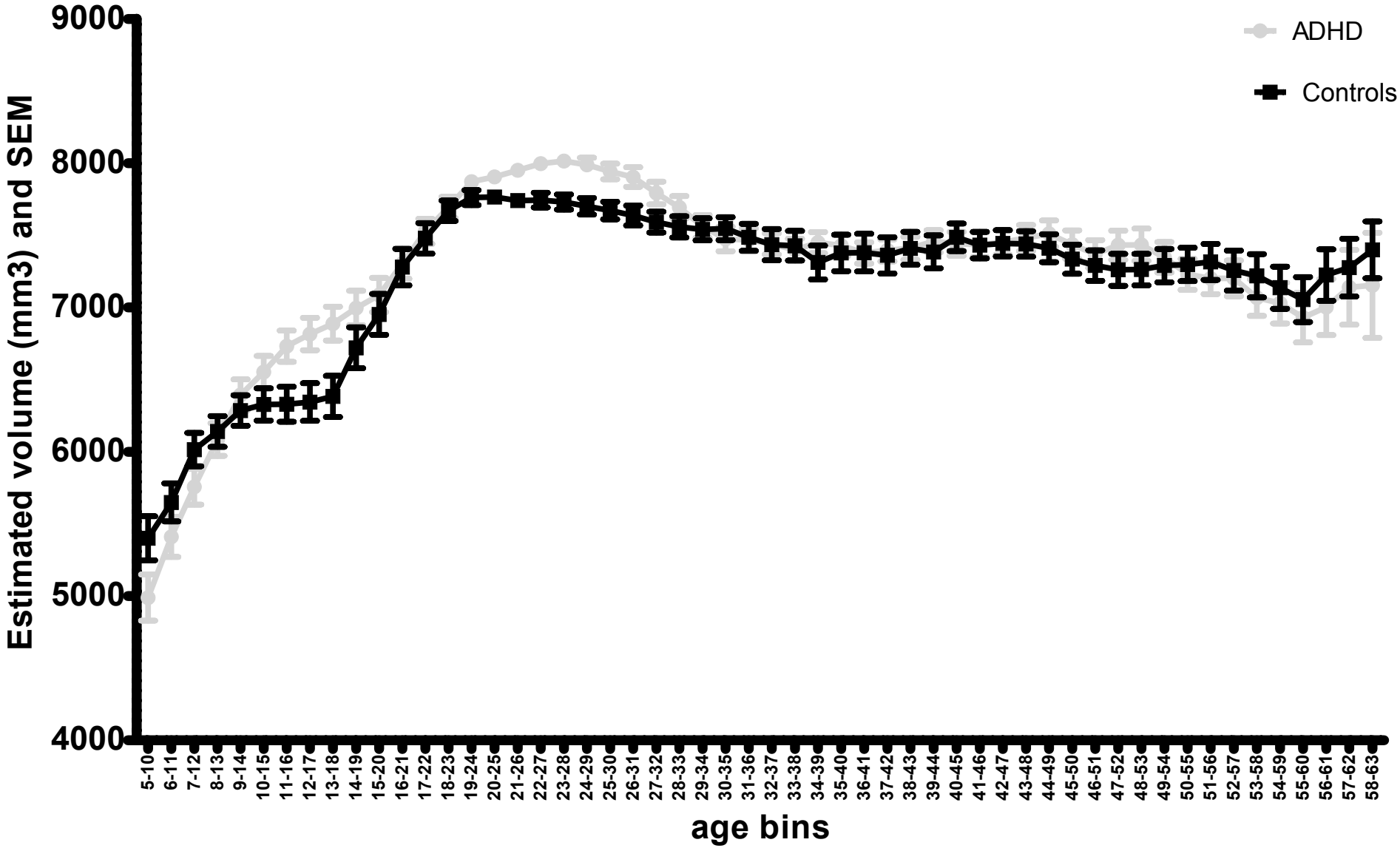
age bins

Thalamus


ADHD
Controls
Estimated volume (mm3) and SEM
9000
8000
7000
6000
5000
4000
5-10
6-11
7-12
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10-15
11-16
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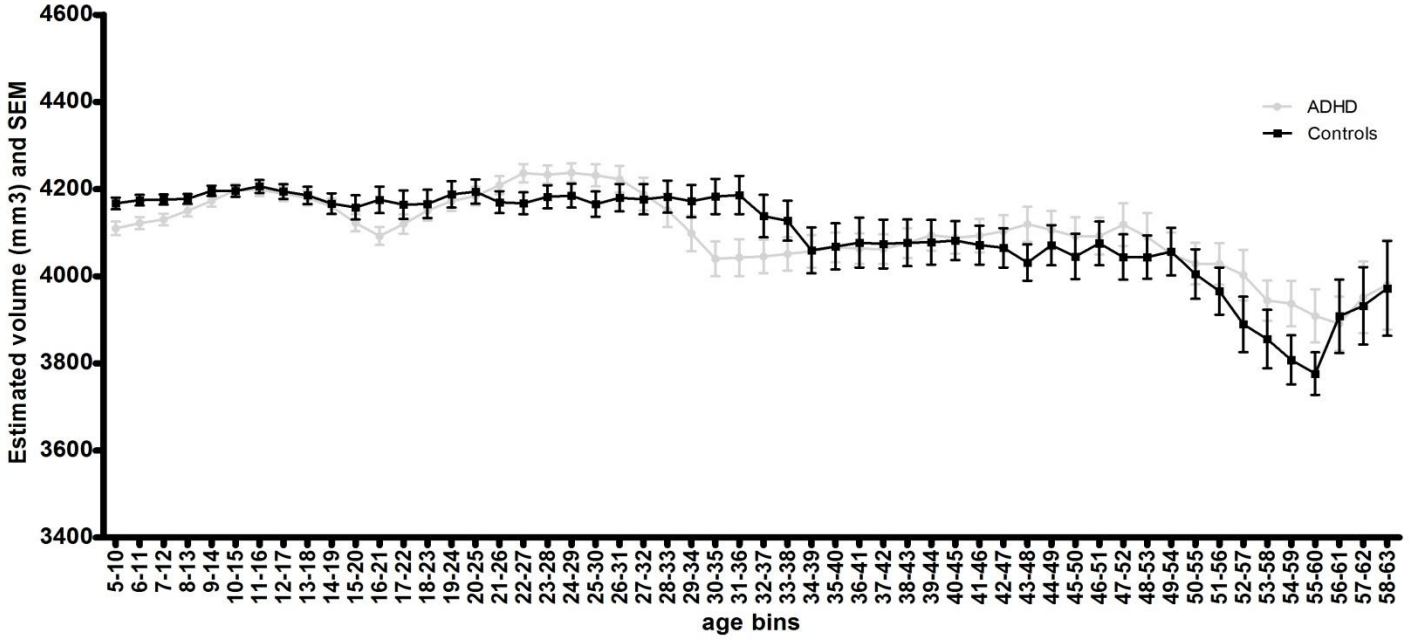
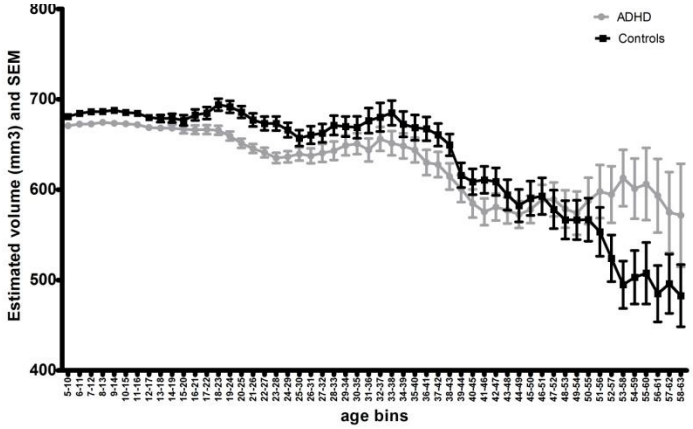
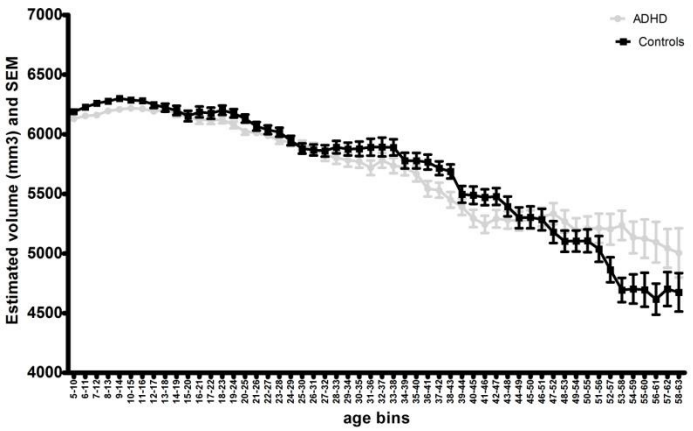
age bins

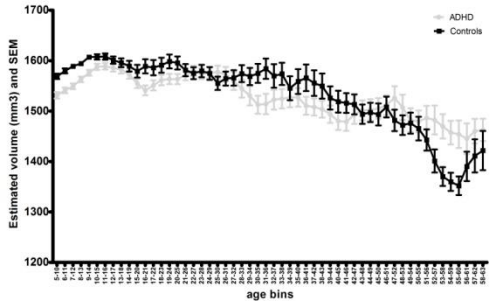
Hippocampus



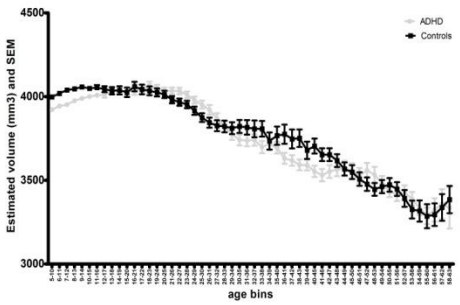




Amygdala



Caudate



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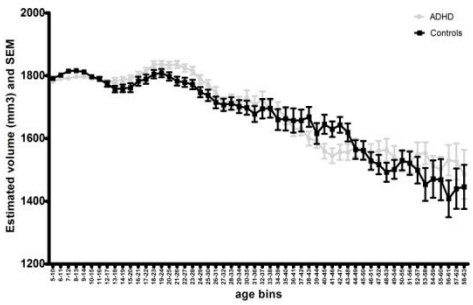
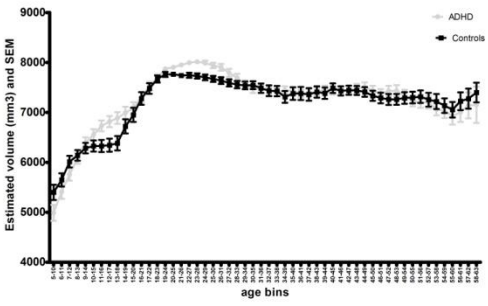


Thalamus



ICV